REMARKS

This Amendment is submitted in response to the final Office Action mailed on August 13, 2009 A petition for a one-month extension of time is submitted herewith. The Director is authorized to charge the amount of $130.00 for the cost of the one-month extension of time, and any additional fees which may be required, or to credit any overpayment to Deposit Account No. 02-1818. If such a withdrawal is made, please indicate the Attorney Docket No. 3712036-00818 on the account statement.

Claims 1-3 and 6-7 are pending in this application. Claims 4-5 and 8-32 were previously canceled without prejudice or disclaimer. In the Office Action, Claims 1 and 3 are rejected under 35 U.S.C. §102. Claims 1-3 and 6-7 are rejected under 35 U.S.C. §112. In response, Claims 1-3 have been canceled. The amendments do not add new matter. At least in view of the amendments and/or for the reasons set forth below, Applicants respectfully submit that the rejections should be withdrawn.

In the Office Action, Claims 1 and 3 are rejected under 35 U.S.C. §102(a) and 102(e) as being anticipated by U.S. Patent Publication No. 2002/0115667 A1 to Walkley et al. ("*Walkley*"). In response, Claims 1-3 have been canceled. Applicants respectfully submit that the cancellation of Claims 1-3 renders the anticipation rejection moot.

Accordingly, Applicants respectfully request that the rejection of Claims 1 and 3 under 35 U.S.C. §102(a) and 102(e) to *Walkley* be withdrawn.

In the Office Action, Claims 1 and 3 are rejected under 35 U.S.C. §102(a) as being anticipated by "Antisense to glucosylceramide synthase in human neuroepithelioma affects cell growth but not apoptosis," Cell Death and Differentiation (2002) 9: 693-695 to Di Sano et al. ("*Di Sano*"). In response, Claims 1-3 have been canceled. Applicants respectfully submit that the cancellation of Claims 1-3 renders the anticipation rejection moot.

Accordingly, Applicants respectfully request that the rejection of Claims 1 and 3 under 35 U.S.C. §102(a) to *Di Sano* be withdrawn.

In the Office Action, Claims 1 and 3 are rejected under 35 U.S.C. §102(a) as being anticipated by "Transfection of glucosylceramide synthase antisense inhibits mouse melanoma formation," Glycobiology vol. 12 no. 3 (2002): 145-152 to Deng et al. ("*Deng*"). In response, Claims 1-3 have been canceled. Applicants respectfully submit that the cancellation of Claims 1-3 renders the anticipation rejection moot.

Accordingly, Applicants respectfully request that the rejection of Claims 1 and 3 under 35 U.S.C. §102(a) to *Deng* be withdrawn.

In the Office Action, Claims 1 and 3 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Publication No. 2002/0142985 A1 to Dwek et al. ("*Dwek*"). In response, Claims 1-3 have been canceled. Applicants respectfully submit that the cancellation of Claims 1-3 renders the anticipation rejection moot.

Accordingly, Applicants respectfully request that the rejection of Claims 1 and 3 under 35 U.S.C. §102(e) to *Dwek* be withdrawn.

In the Office Action, Claims 1 and 3 are rejected under 35 U.S.C. §102(b) as being anticipated by International Patent Publication No. WO 01/36628 A1 to Cabot et al. ("*Cabot*"). In response, Claims 1-3 have been canceled. Applicants respectfully submit that the cancellation of Claims 1-3 renders the anticipation rejection moot.

Accordingly, Applicants respectfully request that the rejection of Claims 1 and 3 under 35 U.S.C. §102(b) to *Cabot* be withdrawn.

In the Office Action, Claims 1 and 3 are rejected under 35 U.S.C. §102(b) as being anticipated by "Uncoupling Ceramide Glycoslyation by Transfection of Glucosylceramide Synthase Antisense Reverses Adriamycin Resistance," Journal of Biological Chemistry vol. 275 no. 10 (2000): 7138-7143 to Liu et al. ("*Liu*"). In response, Claims 1-3 have been canceled. Applicants respectfully submit that the cancellation of Claims 1-3 renders the anticipation rejection moot.

Accordingly, Applicants respectfully request that the rejection of Claims 1 and 3 under 35 U.S.C. §102(b) to *Liu* be withdrawn.

In the Office Action, Claims 1-3 and 6-7 are rejected under 35 U.S.C. §112, first paragraph, for failure to comply with the enablement requirement. The Patent Office asserts that neither the Specification nor the state of the art teaches that a composition which is targeted to and inhibits glucosylceramide synthase treats or prevents any kind of epithelial tissue damage. See, Office Action, page 8, lines 7-11. Specifically, the Patent Office asserts that the only mention of glucosylceramide synthase discloses that reducing the amount of glucosylceramide synthase turns down the signal for epithelial cells to proliferate, but fails to teach that inhibiting glucosylceramide synthase expression treats or prevents epithelial tissue damage. See, Office Action, page 8, lines 14-21.

In response, Applicants note that working examples of a specific embodiment are not required for enablement. For example, the M.P.E.P. clearly states that: "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. . . . The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." See, M.P.E.P. § 2164.02 (2009).

Moreover, Applicants respectfully submit that the portion of the Specification cited by the Patent Office is not the only place where the target molecule glucosylceramide synthase appears. For example, the Specification discloses that glucosylceramides inhibit programmed cell death in the skin and thus affect normal epithelial cell homeostasis:

> Without wishing to be bound to any theory it is currently assumed that ***one of the endogenous tasks of CD_{1d} in living organisms is to directly control normal epithelial cell homeostasis***. Normal skin homeostasis is dependent on the critical and fine tuned balance between epidermal differentiation, apoptosis, proliferation and anti-apoptosis of epidermal cells. ***In the skin, these processes are regulated via lipids, in particular*** by means of ceramides and ***glucosylceramides*** (sphingolipids). While the nucleated cell layers generate glucosylceramides (GlcCer), the proportions of GlcCer to Cer decrease late in epidermal differentiation, with the Cer content peaking in the stratum corneum acting as extracellular constituents of the epidermal permeability barrier. In addition to their structural properties, ceramides are associated with inhibition of cellular proliferation, induction of cellular differentiation and programmed cell death. In contrast, ***GlcCer induce cell proliferation and inhibit programmed cell death***.

See, Specification, page 2, paragraph 35 (emphasis added). Moreover, the Specification teaches:

> It is well established that ceramide glycosylation, via ***glucosylceramide synthase***, and the subsequent build up of glucosylceramides ***allows cellular escape from stress-induced programmed cell death, conferring cancer cell resistance*** of a variety of cancers including breast, ***skin***, colon and ***epitheliod*** carcinomas, to cytotoxic anti-cancer agents.

See, Specification, page 4, paragraph 51, lines 1-6 (emphasis added). Applicants respectfully submit that these portions of the Specification clearly demonstrate to one of ordinary skill in the art that glucosylceramide synthase inhibits the death of damaged or cancerous skin cells and, as such, the reduction of glucosylceramide synthase promotes the destruction of damaged or cancerous skin cells and can thus be used to treat or prevent epithelial tissue damage.

Furthermore, the Patent Office admits that the working examples in the Specification show a relationship between CD_{1d} expression and skin irritation/inflammation. See, Office Action dated February 23, 2009, page 8, lines 19-20. For example, the present Specification teaches that blocking or modifying CD_{1d} activity can be used to treat or prevent tissue damage by replacing damaged skin cells with "healthy" epithelial cells. See, Specification, page 3, paragraphs 37-41. The Specification further teaches that the amount of glucosylceramide synthase transcripts may be reduced "such[] that they exert the desired effect [of blocking or modifying CD_{1d} activity] on the CD_{1d} molecule." See, Specification, page 3, paragraph 45, lines 1-10. One of ordinary skill in the art would therefore understand that reducing the amount of glucosylceramide synthase blocks or modifies the activity of the CD_{1d} molecule and can be used to treat or prevent tissue damage. In fact, the Specification expressly discloses that:

> It is well established that ceramide glycosylation, via glucosylceramide synthase, and the subsequent build up of glucosylceramides allows cellular escape from stress-induced programmed cell death, conferring cancer cell resistance of a variety of cancers including breast, skin, colon and epitheliod carcinomas, to cytotoxic anti-cancer agents. ***As CD_{1d} can bind glucosylceramide*** and is over-expressed by the same multi-drug-resistant cancer cells (e.g squamous cell carcinoma), ***it is envisioned that the anti-apoptotic activity of CD_{1d} regulates cancer cell resistance*** to cytotoxic drugs, ***possibly at the level of protein-glucosylceramide binding***. Thus, in principle the substances of the present invention that block and/or modify endogenous CD_{1d} function strongly decrease multi-drug resistance of a variety of cancers including skin, gut and breast cancers.

See, Specification, page 4, paragraph 51, lines 6-15 (emphasis added).

These portions of the Specification demonstrate to one of ordinary skill in the art that the amount of glucosylceramide synthase is directly related to the activity of the CD_{1d} molecule, and the activity of the CD_{1d} molecule can be blocked or modified in order to treat or prevent epithelial tissue damage. Thus, Applicants respectfully submit that the Specification demonstrates the required nexus between reduction of the amount of glucosylceramide synthase (via an antisense polynucleotide that prevents transcription of the glucosylceramide synthase) and treatment or prevention of epithelial tissue damage. As such, a skilled artisan would be able to practice the present claims 6-7 without undue experimentation.

With respect to the concurrent reduction in the amount of CD1d in a cell required by Claim 6, the Patent Office asserts that "neither the specification nor the state of the prior art establishes the required relationship between reduced glucosylceramide synthase and reduced

CD_{1d}. In fact, contrary to the claimed relationship, . . . it was later found in the art that reduced activity of glucosylceramide. . . results in the increased expression level of CD_{1d}." See, Office Action dated February 23, 2009, page 9, lines 13-22. However, contrary to the Patent Office's assertion, *Balreira* does not show that reduced activity of glucosylceramide results in increased expression of CD_{1d}. Instead, *Balreira* merely demonstrates that a reduced amount of glucocerebrosidase, rather than glucosylceramide synthase, results in an increased surface level of CD_{1d}. See, *Balreira*, Abstract. Unlike glucosylceramide synthase, which generates glucosylceramide, glucocerebrosidase cleaves glucosylceramide into glucose and ceramide. See, *Balreira*, page 667, paragraph 1. As such, a reduced amount of glucocerebrosidase results in an accumulation or excess amount of glucosylceramide. See, *Balreira*, Abstract. Therefore, directly contrary to the Patent Office's assertion, *Balreira* fails to demonstrate that a reduced activity of glucosylceramide results in an increased amount of CD_{1d}.

Accordingly, Applicants respectfully request that the rejection of Claims 1-3 and 6-7 under 35 U.S.C. §112, first paragraph, be withdrawn.

For the foregoing reasons, Applicants respectfully request reconsideration of the above-identified patent application and earnestly solicit an early allowance of same. In the event there remains any impediment to allowance of the claims which could be clarified in a telephonic interview, the Examiner is respectfully requested to initiate such an interview with the undersigned.

Respectfully submitted,

K&L GATES LLP

BY _____
Robert M. Barrett
Reg. No. 30,142
Customer No. 29157
Phone No. 312-807-4204

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